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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/438,206	11/12/1999	RIYI SHI	7024-427-PUR	9018

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EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/438,206	SHI ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's cancellation of claims 1-21 in amendment filed August 29, 2001 is acknowledged.

Applicant's declaration filed August 29, 2001 is also acknowledged.

Applicant's addition of claims 22-43 in amendment filed in August 29, 2001 is acknowledged.

The outstanding rejections of claims 1-8, and 11 under 35 USC 112, first and second paragraph are withdrawn in view of the amendment filed in August 29, 2001.

The outstanding rejection of claims 1-15 under 35 USC 103(a) is removed in view of the Borgens' declaration and the amendment filed August 29, 2001.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment employing the synergistic combination of polyethylene glycol (PEG) and 4-aminopyridine (4-AP), does not reasonably provide enablement for combination of C_3-C_{10} alkylene glycols and other potassium channel blockers.

In the instant case, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define the useful combination of "C_3-C_{10} alkylene glycols" and "potassium channel blockers". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, the only example set forth is the synergistic combination of "PEG and 4-AP", thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the combination of

compounds required. Synergistic effect is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on **all** "potassium channel blockers", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "said method resulting in ... after said spinal cord is treated." in claim 22, lines 4-6 and claim 38, line 2-6 renders the claims indefinite as to method steps required to achieve the recited results.

The expression "as soon as possible" in claims 22 and 38 renders the claims indefinite as to the time of contact between the injured spinal cord and the polyethylene glycol compounds encompassed by the claims.

The recitation "said method resulting in a synergistic increase... behavior in said patient." in claim 30, lines 4-6 renders the claims indefinite as to method steps required to achieve the recited results.

The expression of "**before, during or after** contacting said spinal cord with said polyalkylene glycol" in claims 30 and 40 renders the claims indefinite because it is

unclear how administration of a potassium channel blocker at any time before or after the PEG compound herein may result in synergistic effects between the two agents. For example, is it possible that 4-AP is administered **30 days before** administering PEG to a patient and still expect a synergistic effect?

The term " at least partial restoration " in claim 22 and 38 is a relative term which renders the claim indefinite. The term " at least partial restoration " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims is indefinite as to the degree of restoration encompassed thereby.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22, 24-29, 38-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al. (Journal of Spinal Disorders, 1990;3(4):299-306).

Davis et al. teaches that Depo-Medrol, a depot formulation of methylprednisolone containing PEG 3350 (the product information of Depo-Medrol from PDR, 1996, page 2600-2602 is also provided), is instilled to the exposed nerve root **during** a spinal lumbar surgery for disc excision and retraction of the nerve root with incision (a severed

form of spinal cord injury). Davis et al. further teaches that the procedure leads to a condition of less pain and spasm (See the abstract; and page 300, col. 2, last paragraph), which indicates that the patients' behavioral and neural functions are restored. The claims now recite the limitations of "at least partial restoration of nerve function and an increased behavioral recovery after the spinal cord is treated".

Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to treating a mammalian patient suffered an injury to its spinal cord with polyethylene glycol. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use. Attempts to distance claims from anticipated utilities with specification limitations will not be successful. At page 1391, *Ex parte Novitski*, supra, the Board said "We are mindful that, during the patent examination, pending claims must be interpreted as broadly as their terms reasonably allow. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). As often stated by the CCPA, "we will not read into claims in pending applications limitations from the specification." *In re Winkhaus*, 52 F.2d 637, 188 USPQ 219 (CCPA 1975).". In the instant application, Applicants' failure to distance the proffered claims from the anticipated prophylactic utility, renders such claims anticipated by the prior inherent use.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23, 30-37, and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (Journal of Spinal Disorders, 1990;3(4):299-306) in view of Brown (Clinical Orthopedics and Related Research, 1977;129:72-78) and Potter et al. (Clin Invest Med, 19(4), Suppl.: S80, #533). Potter et al. is of record in the previous office action mailed February 27, 2001.

Davis et al. teaches Depo-Medrol, a depot formulation of methylprednisolone containing PEG 3350, is being instilled to the exposed nerve root **during** a spinal lumbar surgery for disc excision and retraction of the nerve root with incision (a severed form of spinal cord injury). Davis et al. further teaches that the procedures leads to a condition of less pain and spasm which indicates that the patients' behavioral and neural functions are restored. See the abstract; and page 300, col. 2, last paragraph.

Davis et al. does not expressly teach the that 4-aminopyridine, the potassium channel blocker, can be combined with the spinal cord injury treating method of Davis et al. to treat spinal cord cell injury. Davis et al. does not expressly teach that the spinal cord is crushed.

However, Potter et al. teaches the use of 4-aminopyridine to treat spinal cord injury (See #533).

Brown teaches that the treatment of patients with radiculopathy, which is a spinal cord injury in the lower back, caused by mechanical compression of disk prolapse with Depo-Medrol produces a beneficial response (See page 77, Table 1; also page 72, col. 1 and 2).

It would have been obvious to one skill in the art when the invention was made to employ a combination of 4-aminopyridine with polyethylene glycols together to treat mammalian spinal cord injury, including crush injury.

One of ordinary skill in the art would have motivated to employ a combination of 4-aminopyridine with polyethylene glycols herein together to treat mammalian spinal cord injury including crush injuries, because combining two agents which are known to be useful to treat spinal cord injury individually into a single method that is useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. At least additive therapeutic effects are reasonably expected.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed,

In re Linder, 173 USPQ 356 (CCPA 1972). In regard to the unexpected result of the instant invention as asserted by the applicant in amendment filed August 29, 2001, data from examples 1-6 in the specification have been considered because they are the only examples employing crushed spinal cord. These examples are not found persuasive as to the non-obviousness of the instant invention because the increase of CAP by administering PEG on the injured spinal cord is seen to be expected. Example 2 has been considered as to a synergistic effect because it employs both PEG and 4-AP. From the data in Figure 6A –6C, the enhancement of CAP with 4-AP treatment alone is around 40%, which is similar to the enhancement of CAP in the control group. The enhancement of CAP with treatment of 4-AP plus PEG is around 70%. This is seen to be an expected additive effect. No convincing and clear unexpected, supra-additive or synergistic result is seen.

For example, from the data in Figure 3 of the specification, the CAP amplitude of the PEG-treated spinal cord was around 19% as compared to the control of 0%. From the data in Figure 4A-4D, the effects of PEG on the crushed spinal cord are similar to that of the control. Attention is drawn to figures 4B and 4D, the post-injury amplitude of the control group is similar to that of the PEG-treated group. This is also true for the results illustrated in Figures 5 B and C. Moreover, the study design of example 5 in the specification in an attempt to demonstrate behavioral recovery is confusing. It is not clear how the stimuli to the skin would relate to the behavioral recovery of the animal. Example 6 herein attempts to measure the physiological response of SSEP conduction. Data from Figure 13 A-C demonstrate the effectiveness of PEG treatment to a crushed

spinal in terms of the SSEP conduction. The results herein merely shows the expected results over the prior art. There area no labels for each of Figures 14 A-C, so it is unclear which Figure corresponds to 14A, B, or C. The average level is about 40% of the preinjured SSEP amplitude level. The results from examples 1-6 are being expected over the prior art. Unexpected results must be **clear and convincing**. In the instant case, no clear and convincing unexpected result is seen herein.

Borgens' declaration filed August 29, 2001 has been considered as to the non-obviousness of instant invention but are not found persuasive because Borgens' declaration merely discussed the unpredictability of *in vivo* effect from *in vitro* data and therefore the prior art used, which contains data from *in vitro* experiments, in the rejection under 35 USC 103(a) in the previous office action mailed February 27, 2001 would not render the instant invention obvious. However, in light of the new grounds of rejection that are based on prior art containing data from *in vivo* clinical studies, Borgens' declaration filed August 29, 2001 is now rendered moot.

Response to Remarks

Applicant's arguments with respect to claims 22-43 have been considered but are moot in view of the new ground(s) of rejection.

In response to applicant's argument based upon the age of the references, contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed

knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
November 19, 2001

MINNA MOEZIE, J.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600